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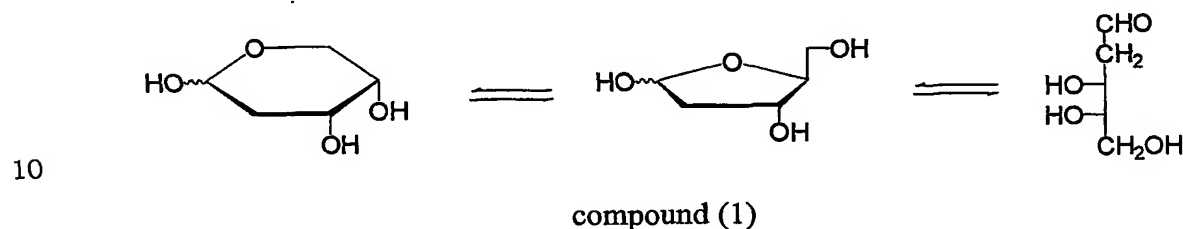
(54) Title: METHOD FOR PRODUCING 2-DEOXY-L-RIBOSE

(57) Abstract: The present invention relates to a economic synthetic method of 2-deoxy-L-ribose from 2-deoxy-D-ribose with easy reaction, separation and purification. The present invention consists of four(4) steps including protection, activation 3-and 4-OH groups, inversion and deprotection step. In respect to the cost for equipment, reagent and operation, by the present invention, 2-deoxy-L-ribose can be produced more economically because the invention uses 2-deoxy-L-ribose which is abundant in nature and easily synthesized from D-glucose, and adopt simple and yielding process.

METHOD FOR PRODUCING 2-DEOXY-L-RIBOSE

TECHNICAL FIELD

5 The present invention relates to a synthetic method for the compound having compound (1) below, more specifically, to a mass-produceable and cost-effective synthetic method of compound (1) from 2-Deoxy-D-ribose with easy reaction, separation, and purification.

BACKGROUND ART

15 Recently, natural or modified L-nucleoside are attracting attention as antiviral agents. Some L-nucleosides such as L-thymidine, L-2'-thiacytidine (3TC) and L-2',3'-dideoxycytidine (L-ddC) are much less toxic and have better antiviral activity than their D-isomers. In addition, L-nucleosides have good effect in antisense oligonucleotide therapy.

20

For the above reasons, many attempts have been made to synthesize L-nucleosides effectively which cannot be obtained as natural products. The efforts has been being

focused to economic and mass-produceable preparation method for the derivatives of L-sugar, particularly, 2-deoxy-D-ribose and L-ribose which can be used as key intermediates of L-nucleosides.

5 Some synthetic methods for 2-deoxy-L-ribose are known from D-ribose, L-arabinose or L-ascorbic acid. (WO 9839347, CS 274394B1, Nucleosides Nucleotides 1999, 18 (11 & 12), 2357-2365, Tetrahedron: Asymmetry 2000, 11, 1869-176, Org. Lett 1999, 1 (10), 1517-1519)

10 In these methods, however, expensive or highly toxic reagents are used; difficult separation and purification is required; the overall yield is low; all which are obstacles to the application in the large-scale synthesis.

DISCLOSURE OF INVENTION

15 Accordingly, the objective of the present invention is to provide a synthetic process of 2-deoxy-L-robse, which allows the cost-effective and large-scale synthesis thanks to the short process, the easy reaction and purification.

BEST MODE FOR CARRYING OUT THE INVENTION

20 To achieve the above objective, the present invention provides the synthetic process of compound (1) comprising 4 steps; protection, activation and inversion of 3- and 4-OH groups of 2-deoxy-D-ribose, and deprotection.

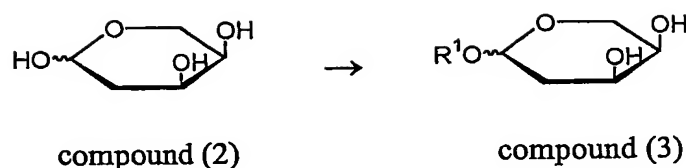
The present invention provides the synthetic process of compound (1) comprising the steps of; (A) protection step in which aldehyde group of 2-deoxy-D-ribose is protected in the form of acetal. 2-deoxy-1-O-alkyl-D-ribopyranoside is prepared by the reaction of 2-deoxy-D-ribose with alcohol in the presence of acid; (B) activation step
5 in which 3- and 4-OH groups of 2-deoxy-D-ribose are activated. 2-deoxy-1-O-alkyl-3,4-di-(alkanesulfonyl)-D-ribose or 2-deoxy-1-O-alkyl-3,4-di-(arylsulfonyl)-D-ribose is prepared by reaction of the above 2-deoxy-1-O-alkyl-D-ribose with organic sulfonylhalide for activation of 3- and 4-OH; (C) inversion step in which stereochemistry of 3- and 4-OH groups is changed. Reaction of the above 2-deoxy-1-
10 O-alkyl-3,4-di-(alkanesulfonyl)-D-ribose or 2-deoxy-1-O-alkyl-3,4-di-(arylsulfonyl)-D-ribose with a metal salt of organic acid leads to 2-deoxy-L-ribose derivatives of which stereochemistry of 3- and 4-OH is different from the corresponding 2-deoxy-D-ribose derivatives; (D) deprotection step in which 2-deoxy-L-ribose is prepared by consecutive reactions of the step (C) products with acid and base.

15

Each step will be explained in the following.

(1) Protection

20 In this step, protecting group is introduced in the form of acetal by the reaction of compound (2), 2-deoxy-D-ribose with alcohol in the presence of acid.

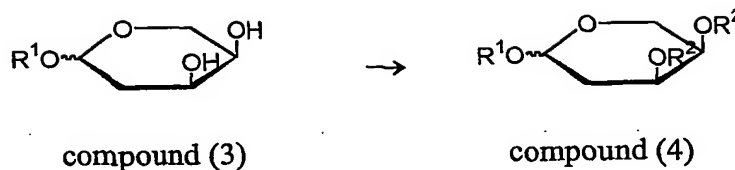


Here, R1 represents a lower alkyl having 1-5 of carbon number, a benzyl or a substituted benzyl. The acid used in this step contains inorganic acid such as hydrochloric acid and sulfuric acid or organic acid such as methanesulfonic acid and p-toluenesulfonic acid and the concentration of acid is preferably 1 ~ 10%. A lower alcohol such as methyl alcohol, ethyl alcohol, propyl alcohol and butyl alcohol, benzyl alcohol or substituted benzyl alcohol may be used.

(2) Activation of 3- and 4-OH groups: Preparation of 2-Deoxy-1-O-alkyl-3,4-di-(alkanesulfonyl)-D-ribose or 2-deoxy-1-O-alkyl-3,4-di-(arylsulfonyl)-D-ribose

In this step, compound (4), 2-deoxy-1-O-alkyl-3,4-di-(alkanesulfonyl)-D-ribose or 2-deoxy-1-O-alkyl-3,4-di-(arylsulfonyl)-D-ribose is obtained by converting 3- and 4-OH groups of compound (3) into 3- and 4-sulfonyl groups by the action of organic sulfonyl halide and an organic base. The purpose of this reaction is the activation of 3- and 4-OH groups for further reaction.

An organic sulfonyl halide used in this step may include a lower alkanesulfonyl halide such as methanesulfonyl chloride and trifluoromethylsulfonyl chloride and arylsulfonyl halide such as benzenesulfonyl chloride and p-toluenesulfonylchloride. Detailed reaction condition is accordance with basic methods of organic synthesis.



Here, R1 represents a lower alkyl having 1-8 of carbon number, a substituted or
 5 unsubstituted benzyl and R2 represents a lower alkylsulfonyl having 1-8 of carbon
 number, a substituted or unsubstituted aryl sulfonyl group.

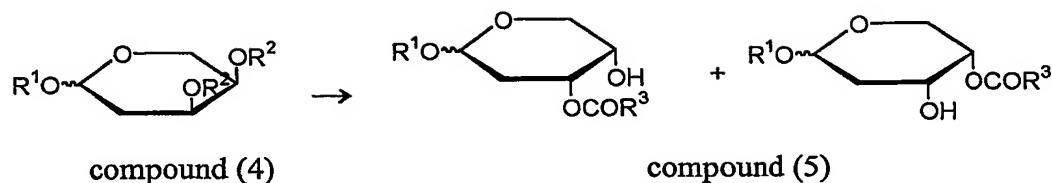
(3) Inversion (conversion to L-sugar from D-sugar): Preparation of the mixture of 2-
 deoxy-1-O-alkyl-3-acyl-L-ribose and 2-deoxy-1-O-alkyl-4-acyl-L-ribose

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Compound (5), the mixture of 2-deoxy-1-O-alkyl-3-acyl-L-ribose and 2-deoxy-
 1-O-alkyl-4-benzoyl-L-ribose in which the stereochemistry of 3- and 4- carbon is
 changed is prepared through the reaction of compound (4) with a metal salt of organic
 acid.

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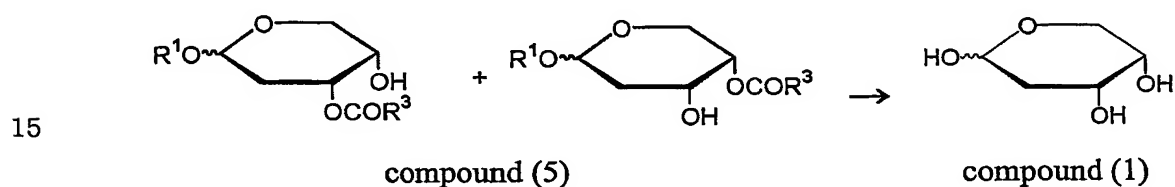
A metal salt of organic acid used in this step may include a metal salt of lower
 alkyl organic acid such as sodium acetate, potassium acetate or a metal salt of aryl
 organic acid such as sodium benzoate or potassium benzoate. A solvent used in this
 step may include water and organic solvent such as dimethylformamide (DMF),
 20 dimethylacetamide (DMAC), and alcohols, but DMF or the mixture of water and
 organic solvent is preferable in view of solubility of the reactants.



Here, R1 represents a lower alkyl having 1-8 of carbon number, a substituted or
 5 unsubstituted benzyl and R2 represents a lower alkylsulfonyl having 1-8 of carbon
 number, a substituted or unsubstituted aryl sulfonyl group.

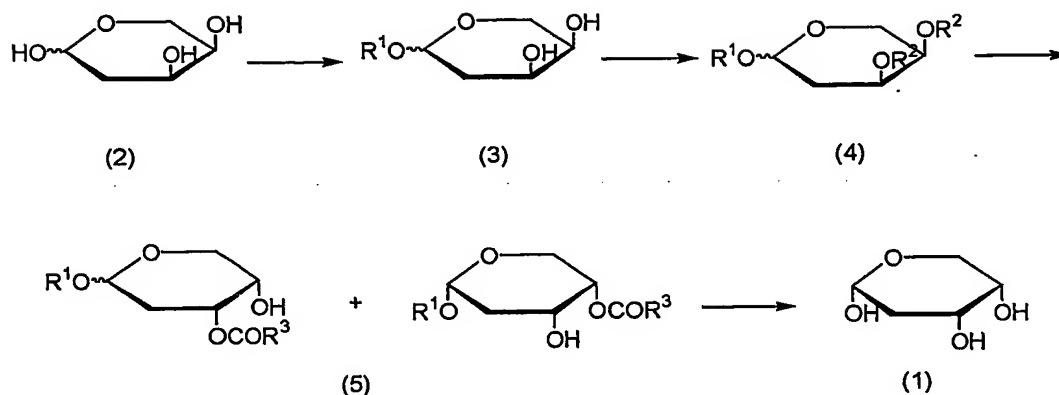
(4) Deprotection

10 Compound (1), 2-deoxy-L-ribose is obtained by the stepwise reactions of
 compound (5) with acid and base. Acid and base used in deprotection conventionally
 may also be used in this step. The order of the stepwise reactions may be changed
 according to its convenience.



Compound (1) can be used as a raw material for the further reaction without
 purification or can be purified by the formation of anilide derivative well known as a
 20 purification method of 2-deoxy-D-ribose to obtain as solid

The above preparation method is depicted in the following scheme:



[R1: lower alkyl having 1-8 of carbon number or substituted or unsubstituted benzyl

5 R2: lower alkylsulfonyl having 1-8 of carbon number or substituted or unsubstituted arylsulfonyl

R3: lower alkyl having 1-8 of carbon number or substituted or unsubstituted benzyl]

10 The syntheses described above provide simple preparation method of compound (1) utilizing chief and commercially available reagents without toxic reagent such as heavy metal and easily attainable temperature and pressure range.

In addition, separation and purification is easy without special equipment because the key intermediate and final product can be purified by recrystallization.

15

The raw material, 2-deoxy-D-ribose is not only abundant in natural products, but also obtained by chemical synthesis. All the above reason make the procedure mass-producible effectively.

To assist in understanding the present invention more clearly, the following embodiments are appended. The embodiments should not, of course, be construed to limit or alter the scope of the present invention. Further, the variations or modifications of the present invention which do not depart from the spirit of the present invention can easily be made by one of ordinary skill in the art and are considered to fall within the scope of the present invention.

PREFERRED EMBODIMENTS

10 **Embodiment 1**

Protection: Preparation of 2-deoxy-1-O-butyl-D-ribose

To a cooled butyl alcohol containing 3% HCl (56.4 mL) was added 2-deoxy-D-robse (10g) and stirred under -2°C for 16 hours. The reaction mixture was neutralized with triethylamine keeping the temperature under 10 °C and stirred at 20 ~ 25°C. The mixture was filtered and washed with acetone (20 mL). The combined filtrate and washing solution was concentrated and used for further reaction without purification.

Embodiment 2

20 **Activation of 3- and 4-OH groups: Preparation of 2-Deoxy-1-O-butyl-3,4-di-(p-toluenesulfonyl)-D-ribose**

To the solid of 2-deoxy-1-O-butyl-D-ribose obtained in Embodiment 1 were added pyridine (36 mL), p-toluenesulfonyl chloride (42.6g) stepwise under 30°C and

the mixture was stirred at 27 ~ 30 °C for 20 hours. The reaction mixture was heated to 75±2 °C and stirred for 2 hours. After the completion of reaction, the mixture was cooled to 15 ~ 20 °C and purified water (30mL) was added and the resulting mixture was extracted twice with ethyl acetate (30mL). The extract was concentrated and ethyl alcohol and isopropyl alcohol were added. The solution was cooled, filtered, and dried, to obtain the solid of 2-deoxy-1-O-butyl-3,4-di-(p-toluenesulfonyl)-D-ribose (23g).

Embodiment 3

10 **Conversion to L-form sugar from D-form sugar: Preparation of 2-deoxy-1-O-butyl-3-benzoyl-L-ribose and 2-deoxy-1-O-butyl-4-benzoyl-L-ribose**

To the compound obtained in Embodiment 2 (20g) were added n-butanol (7 mL), water (4.4mL), N,N-dimethylformamide (27.6 mL) and potassium benzoate (21.2g) and the mixture was heated to 115°C and reacted for 8 hours. After the concentration of the reaction mixture, water and ethyl acetate were added to separate organic and water layers. After the organic layer was concentrated, the residue was mixed with water and evaporated again to concentrate N,N-dimethylformamide efficiently. The residue was used for the next reaction.

20

Embodiment 4

Deprotection: Preparation of 2-deoxy-L-ribose

To the residue obtained in Embodiment 3 were added water (10 mL) and 40% sodium hydroxide solution (10 mL) and the mixture was stirred for 3 hours at room

temperature. 6N hydrochloric acid (50mL) was added to the reaction mixture and the resulting mixture was stirred for 4 hours at 25 ~ 30 °C to give 2-deoxy-L-ribose. Through the formation of anilide derivative which was already known for its enantiomer 2-deoxy-D-ribose, pure 2-deoxy-L-ribose was obtained as solid (3.4g).

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INDUSTRIAL APPLICABILITY

The present invention is related to the synthetic method for 2-deoxy-L-ribose in which reaction and purification is easy at easily attainable range of temperature and pressure, and of which reagents are more cheap and less toxic. Additionally, this invention provides more economic method than the previously known process in terms of the costs for equipments, raw-materials, and processing by using the low-cost and non-toxic reagents starting from 2-deoxy-D-ribose which is naturally abundant as well as can be synthesized from D-glucose easily.

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What is claimed is:

1. A method for producing 2-deoxy-L-ribose comprising the steps of

(A) protection step for preparation of 2-deoxy-1-O-alkyl-D-ribopyranoside, of
5 which the aldehyde group in 2-deoxy-D-ribose is protected in the form of acetal, by
reacting 2-deoxy-D-ribose with an alcohol in the presence of an acid;

(B) activation step for preparation of 2-deoxy-1-O-alkyl-3,4-di-(alkanesulfonyl)-
D-ribose or 2-deoxy-1-O-alkyl-3,4-di-(arylsulfonyl)-D-ribose, of which the 3- and 4-
OH groups in 2-deoxy-D-ribose are activated, by reacting the above 2-deoxy-1-O-
10 alkyl-D-ribose and an organic sulfonyl halide in the presence of a base;

(C) inversion step for preparation of a mixture of 2-deoxy-1-O-alkyl-3-acyl-L-
ribose and 2-deoxy-1-O-alkyl-4-acyl-L-ribose, in which the stereochemistry of 3-OH
and 4-OH groups are inverted, by reacting the above 2-deoxy-1-O-alkyl-3,4-di-
(alkanesulfonyl)-D-ribose or 2-deoxy-1-O-alkyl-3,4-di-(arylsulfonyl)-D-ribose with a
15 metal salt of organic acid; and

(D) deprotection step for preparation for 2-deoxy-L-ribose by reactions of the
above mixture of 2-deoxy-1-O-alkyl-3-acyl-L-ribose and 2-deoxy-1-O-alkyl-4-acyl-L-
ribose with an acid and then with a base, or with a base and then with an acid.

20 2. The method for producing 2-deoxy-L-ribose according to Claim 1, wherein the
alcohol used in said protection step is a lower alcohol having 1-4 of carbon number,
benzyl alcohol or substituted benzyl alcohol.

3. The method for producing 2-deoxy-L-ribose according to Claim 1, wherein the

organic sulfonyl halide used in said activation step is a lower alkanesulfonyl halide such as methane sulfonyl chloride or trifluoromethyl chloride, or arylsulfonyl halide such as benzenesulfonyl chloride or p-toluenesulfonyl chloride.

- 5 4. The method for producing 2-deoxy-L-ribose according to Claim 1, wherein the metal salt of organic acid used in said conversion step is a metal salt of lower alkyl organic acid having 1-8 of carbon number or a metal salt of aryl organic acid.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR03/01398**A. CLASSIFICATION OF SUBJECT MATTER****IPC7 C07H 3/02**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC C07H 3/*

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean Patents and applications for inventions since 1975Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
KIPASS, USPTO, PAJ**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98/ 39347 A2 [Univcity of California] 11 Septemer 1998. see the whole document.	1
A	US 5,659,021 A [Abushanab, Peace Dale] 19 August 1997. see the whole document.	1
A	US 5,220,003 A [Univcity of California] 15 June 1993. see the whole document.	1
A	US 4,675,390 A [Eli Lilly & Company] 23 June 1987. see the whole document.	1
A	KR 1994-701406 A [Antivirals Inc] 28 May 1994. see the whole document.	1
A	KR 2000-008131 A [Jung Nak - sin] 07 February 2000. see the whole document.	1

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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Date of the actual completion of the international search

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Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR03/01398

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